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MUTUAL PHARMACEUTICAL'S SUPPLEMENTAL SUBMISSION IN SUPPORT OF PETITION FOR STAY OF ACTION

A. ACTION REQUESTED

On behalf of Mutual Pharmaceutical Co., Inc. ("Mutual"), the undersigned hereby submits this supplemental submission in support of its above-referenced Petition for Stay of Action (2004P-0140/PSA2) submitted on April 5, 2004 under section 505 of the Federal Food, Drug and Cosmetic Act (FDCA), and 21 C.F.R. § 10.35. Mutual's Stay Petition is directed at King's previously filed Stay Petition and related Citizen petition (filed March 18, 2004, supplemented April 15, 2004), and specifically to the supplemental NDA (sNDA) relied upon in support of those Petitions. King's sNDA seeks to make changes to the labeling of its Skelaxin (metaxalone) tablets drug product to recommend dosing the drug with food, and King relies upon FDA's determination that its sNDA is "approvable" in support of its Petitions. However, there are serious legal and scientific concerns as to the appropriateness of FDA's "approvable" determination, and of any decision to grant final approval of King's proposed labeling changes. Thus, Mutual's Stay Petition requested that FDA stay approval of King's sNDA until the Agency has responded to King's Citizen petition, and more specifically that FDA:

(a) Rescind, and/or *stay* the effect of, the March 12, 2004 "approvable" letter to King for NDA 13-217/S-046;

(b) *Stay* any approval of new Skelaxin labeling that recommends, requires, or otherwise discusses dosing the drug with food, either generally or for any subset of patients;

2004P-0140 SUP 2

(c) *Stay* approval of any Skelaxin labeling changes until FDA:

> **(i)** has published the full text of the pending requested Skelaxin labeling changes, the clinical data submitted by King in support of the requested changes, and all clinical data and correspondence between Elan or King, and FDA, regarding proposed changes in the Skelaxin labeling since 2000; and
>
> **(ii)** has accepted and considered comments from interested persons, submitted within 60 days of the publication of the information described in subparagraph (i) above, with respect to the validity and relevance of King's requested changes to the Skelaxin labeling, and any changes that may be necessary to allow generic applicants to carve out any protected information and allow immediate final approval of metaxalone ANDAs.

As noted, in support of its own Citizen Petition and Petition for Stay of Agency Action, King refers to and relies upon several food effect bioavailability studies submitted in support of its pending labeling supplement. This reliance in support of its Petitions obviously reflects King's belief that the studies are relevant to the issues posed in this public proceeding – i.e., whether metaxalone labeling must reflect fed-dosing information – and thus requires FDA and King to make all of those studies a matter of public record. *See* 21 C.F.R. § 10.30(i)(1) ("The record of the administrative proceeding consists of the following: (1) The petition, including all information on which it relies....") (emphasis added). Thus, FDA cannot lawfully grant King's Petitions without making the full data and reports of *all* of King's metaxalone studies, whether previously reported or not, available for public review and comment. As those studies are also highly relevant to FDA's consideration of Mutual's Stay Petition, Mutual is entitled to review those studies and comment further in connection with its Stay Petition. Neither King nor FDA has made those bioavailability studies available, and Mutual thus calls upon the Agency and King to do so expeditiously.

Notwithstanding King's improper withholding of its Skelaxin food effect studies, the description and discussion of those studies in King's Petitions, and in the currently approved Skelaxin labeling, demonstrate that the studies are wholly inadequate to support any clinical rationale for inclusion of a fed dosing instruction for Skelaxin. Moreover, as discussed in this supplemental submission, extensive data in the scientific literature demonstrates that food-drug interactions (food effects) are highly dependent on the specific composition of the food with which the drug is dosed. As is evident from King's previous submissions, the Skelaxin studies were conducted using only a "standardized high fat meal" for the fed-dosing arms, and therefore fail to provide sufficient data for FDA to reach any meaningful conclusion as to whether a generalized fed dosing instruction is appropriate for metaxalone products. Accordingly, this supplemental submission further requests that FDA:

> **(d)** Reexamine the adequacy of King's bioavailability studies in light of the information and data presented herein, and ***refuse to approve*** any Skelaxin labeling changes that would recommend dosing the product with food, either generally or for any subset of patients; or alternatively,

(e) Require changes to the Skelaxin labeling to instruct all patients to take the drug on an empty stomach if FDA determines that new dosing and administration instructions are desirable in light of metaxalone's food effect.

B. SUPPLEMENTAL STATEMENT OF GROUNDS

1. Background

In March 2002 Elan (the prior owner of the Skelaxin NDA) sought Skelaxin labeling changes that would include information about the food effect of metaxalone, and specifically sought labeling that described increased bioavailability of metaxalone when dosed with food. The intent was obvious – Elan had received a patent purporting to cover a method of using metaxalone with food to increase bioavailability and it wanted labeling that generic competitors could not copy without filing a Paragraph IV ANDA and being sued by Elan for infringement. FDA approved new labeling to include the fed-dosing bioavailability information but, to Elan's obvious dismay, FDA also required it to change the labeling to include the recommendation that Skelaxin only be dosed on an empty stomach. *See* Approval Letter to NDA #13-217/S-044 (May 31, 2002) (Exhibit A).[1] This approach put an obvious cloud over Elan's effort to block generic competition, because instructions to dose Skelaxin on an empty stomach would not fall within the scope of Elan's patent claims. Thus, Elan quickly objected to this dosing change on the basis that its studies did not demonstrate any clinical relevance to the observed food effects, and thus a fasted-only dosing instruction was not warranted. *See* "REVISED Response to FDA Request for Information" June 7, 2002 (Exhibit 12 to King's Citizen petition) (noting that "it was mutually acknowledged that there [is] no clinical data available that could provide specific guidance" on the clinical relevance of the food effect.) (emphasis added).[2] FDA accepted Elan's proposed labeling changes, which deleted the fasted-dosing instruction and added the statement that "the clinical relevance of these [food] effects is unknown." *Id.*

A fuller understanding of Elan's/King's motivation in objecting to the fasted-dosing instructions initially approved by FDA was made possible by King's Citizen Petition, and its Supplemental Submission to that Petition (filed April 15, 2004), which disclosed that additional bioavailability studies were underway to test for age- and gender-specific food effects of metaxalone in hopes of convincing FDA to include a fed-dosing instruction in

[1] King has failed to include a copy of this letter as an exhibit to any of its submissions in this matter, despite its obvious relevance and importance.

[2] King has also failed to include the original version of this "REVISED" submission to FDA, nor has King submitted any minutes or notes from the various meetings with FDA surrounding these labeling change proposals, thus raising the concern that King is attempting to sanitize the administrative record with respect to the interactions that led to the reversal of FDA's initial fasted-dosing decision. Mutual calls upon King and FDA to make available the *entire* record of Elan's interactions with the Agency in order to assure a full and complete understanding and debate as to the issues involved herein.

Skelaxin labeling. *See* King Citizen Petition at 7-9 and Exhibit 5 thereto. Specifically, based on the results of additional small bioavailability studies (44 and 48 volunteers respectively), and a "meta-analysis" of those studies and Elan's prior food effect studies, King represented to FDA that: bioavailability is always statistically significantly higher in females than in males; in the fasted state bioavailability increases with age; and that in the fed state, age has no effect on bioavailability. King Citizen Petition at 8. Thus, King has requested that FDA amend the Skelaxin labeling "to recommend that Skelaxin be administered with food to ensure more consistent plasma levels of metaxalone." *Id.* FDA issued an "approvable" letter for this change on March 15, 2004.

Final approval of a fed dosing instruction would not only be inappropriate, it could cinch the noose around the necks of generic applicants such as Mutual by bringing all dosing of Skelaxin within the purported scope of King's patents and potentially forcing generic applicants to wait, at a minimum, for the end of the costly and lengthy infringement actions initiated by King. However, as discussed below, the Elan studies – whether individually, in the aggregate, or meta-analyzed – are wholly insufficient to support any clinical efficacy or safety need for fed-dosing instructions for Skelaxin.[3] Moreover, it is doubtful, at best, whether the Elan studies accurately and adequately identify the true pharmacokinetic characteristics of metaxalone, or support the proposition that fed dosing would lead to more consistent metaxalone blood levels.

2. Elan's Studies Did Not, and Could Not, Measure Differences In Clinical Efficacy or Safety Due to the Food Effect of Metaxalone

The bioavailability studies submitted by Elan in support of the addition of new pharmacokinetic information on the food effect of metaxalone did not measure safety or side effects of any kind, nor did they compare efficacy as between fed and fasted dosing regimens. Nor is it appropriate, as King seems to suggest by seeking dosing instruction changes based on those studies, to *presume* a clinical effect based solely on the observed pharmacokinetic effect. Indeed, it is widely accepted in the field of clinical pharmacology that in order to evaluate the clinical relevance of a food-drug interaction, the impact of food intake on the *clinical effect* of a drug must be specifically quantified. Blood level measurements, which is all that King has submitted to its NDA, are not a measure of clinical effect. *See* Schmidt, et al., Food-Drug Interactions, *Drugs*, 62(10): 1481-1502 (2002) (Exhibit C).

[3] Skelaxin is widely regarded as a safe drug. As FDA's medical review of Skelaxin in 2002 noted, for the 30 year period between 1970 and 2000, only 52 Skelaxin-related adverse events were reported to the AERS system, only 18 of those events were serious, and "many were confounded by concomitant medication, preexisting medical conditions or lack of clinical detailed information." *See* Exhibit B. The FDA Medical review also reported several suicide attempts using massive doses of the drug, but one such subject actually survived despite ingesting an estimated 200-250 Skelaxin tablets - *25-30 times greater* than the maximum labeled daily dose.

Variations in pharmacokinetic parameters do not measure (much less prove the existence of) variations in pharmacological effects; food-induced changes in the bioavailability of a drug, standing alone, at most suggest a potential food-drug interaction. *Id.* The clinical relevance of any given food-drug interaction can only be evaluated if the impact of food intake on the clinical effect of the drug is quantified. It is well known that for many drugs with a known food effect, the effect is not associated with any major changes in clinical effect (*e.g.*, pravastatin, phenoxymethylpenicillin and furosemide). *Id.* Thus, bare-bones information on bioavailability, such as submitted by King, utterly fails to make a nexus between clinical relevance and food-drug interactions.

More specifically, the Elan/King biostudies, and the Skelaxin labeling, provide no information whatsoever to even suggest, much less demonstrate by "substantial evidence," that there is any clinical relevance to the metaxalone food effects. Those studies fail to show whether fasted dosing is "safer" or more "effective" than fed dosing, or vice-versa. Indeed, the Skelaxin labeling specifies that there is no known clinical relevance to the observed food effect.[4] More to the point, the bioavailability/food effect studies currently described in the Skelaxin labeling and King's Citizen Petition cannot be considered to have been safety or efficacy studies, as there were no clinical endpoints measured. The Agency's responses to the submission of the initial Elan studies in support of the 2002 Skelaxin labeling changes bear this out because:

> (1) no changes were made to any of the warning, precaution, or contraindication sections of the Skelaxin labeling;
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> (2) no changes to the recommended dosing instructions for Skelaxin were ultimately approved[5]; and
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> (3) the approved Skelaxin labeling states in two separate places that "*The clinical relevance of these [food] effects is unknown.*"

The fact that FDA did not ultimately approve any specific dosing instructions with respect to food is in fact dispositive as to the absence of any safety or efficacy concern, because FDA's own Final Guidance on food effect bioavailability studies only contemplates food-specific dosing and administration instructions where the food effect in fact causes a safety or efficacy concern:

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[4] *See also* King Citizen Petition, Docket No. 2004P-0140/CP-1 (March 18, 2004) at Ex. 6, p. 3, n. 3, noting that no study has been submitted by King "to demonstrate a clinical effect arising from the difference in fed- and non-fed-state bioavailability."

[5] As discussed above, there was a brief one-month period during which the approved Skelaxin labeling required dosing on an empty stomach, but the fact that FDA rescinded this dosing instruction further reflects that the food effect cannot be considered to raise a safety concern.

> The effect of food on the absorption and BA of a drug product should be described in the CLINICAL PHARMACOLOGY section of the labeling. In addition, the DOSAGE AND ADMINISTRATION section of the labeling should provide instructions for drug administration in relation to food based on clinical relevance **(i.e., whether or not the changes in systemic exposure caused by co-administration with food results in safety or efficacy concerns**, or when there is no important change in systemic exposure but there is a possibility that the drug substance causes GI irritation when taken without food).

Guidance for Industry, *Food-Effect Bioavailability Studies and Fed Bioequivalence Studies* at 7 (December 2002) (emphasis added).

Here, the Agency has already properly concluded that the type of small-scale biostudies conducted by Elan do not allow for any finding of safety or efficacy changes (or even "concerns") for metaxalone. In order to support a finding of a safety or efficacy effect based on the food effect, the clinical relevance of alternative dosing regimens (with and without food) would have to be supported by extensive well-controlled clinical trials, in large numbers of patients, that study the effects of the drug on relevant clinical parameters. For instance, FDA approved Flexeril (cyclobenzaprine HCl), a drug that treats skeletal muscle spasms, based on double-blind controlled clinical studies in 1,405 patients that studied the effects of the drug on clinical parameters such as muscle spasm, local pain, local tenderness, limitation of motion, and restriction of activities in daily living. See Flexeril NDA 17-821/S-045, available at <http://www.fda.gov/cder/foi/label/2003/17821se8-045_flexeril_lbl.pdf>. Furthermore, any such studies would have to incorporate full analyses of any adverse events occurring as a result of food-drug interactions.

King has failed to conduct any such studies, yet now seeks to add a fed-dosing instruction based on two small-scale bioavailability studies, and a "meta-analysis" of those studies and the prior studies that were already deemed inadequate to support a dosing instruction change. King simply cannot have it both ways, and for FDA to now approve a fed-dosing instruction based on the paucity of relevant evidence before it would be medically unfounded, arbitrary and capricious.

3. There Is No Basis to Impose a Fed Dosing Instruction "To Ensure More Consistent Plasma Levels of Metaxalone"

King appears to recognize that its studies do not and cannot support any clinically-based changes to the Skelaxin dosing instructions, and have therefore attempted to justify the requested fed-dosing instructions on the premise that such dosing would "ensure more consistent plasma levels of metaxalone." King Citizen Petition at 8. As discussed above, such a change is not only medically and legally unjustified, but as explained below, it does not even appear to be the case that such a dosing instruction would achieve the purported goal of more consistent metaxalone blood levels. Thus, FDA should refuse to approve King's sNDA 13-217/S-046.

(a) King's Studies Are Unreliable Because They Failed to Account For Potentially Significant Differences in the Type of Meal Used in the Fed-Dosing Arms

The bioavailability studies submitted in support of King's requested label changes for Skelaxin compare the oral bioavailability of Skelaxin under fasted conditions and under fed conditions in which healthy volunteers were fed a "standardized high-fat meal." King Citizen petition at 6 (emphasis added). The initial Elan studies showed that under the latter conditions, bioavailability as measured by peak plasma concentration (Cmax), time to Cmax after dosing (Tmax), and area under the plasma concentration time curve ($AUC_{0\text{-}inf}$) were higher for the high-fat fed conditions. A significant deficiency of those studies, however, is that they did not study dosing regimens that approximate the varying dietary patterns commonly seen in the American population in general (for example: low-fat; high-protein; high-fat/high protein/low-carbohydrate (the popular Atkins diet and its various derivatives); vegetarian; diabetic; *etc.*). Nor do the studies account for varying eating patterns for any individual, for example, an individual who eats a low fat meal for breakfast (e.g., oatmeal, pancakes, etc.), a high fat lunch (e.g., a Big Mac®, french fries, and milkshake), and a low fat dinner (e.g., grilled salmon and rice).[6]

As demonstrated below, the failure to account for varying dietary patterns is a fatal flaw in King's effort to obtain a fed dosing instruction for Skelaxin. This is because extensive studies on various drugs have shown that oral bioavailability can be strongly influenced not only by food-drug interactions generally, but also by the specific composition of the food ingested during a dosing regimen. In effect, different food types can have widely divergent effects on the oral bioavailability of drugs. The literature is replete with studies that indicate that the bioavailability of drugs is significantly influenced by fat, protein, and carbohydrate content – alone or in combination – in meals accompanying a dosing regimen.

For instance, some studies have shown that bioavailability is greater following a low fat meal than a high fat meal. *See* Martinez et al., Effect Of Dietary Fat Content On The Bioavailability Of A Sustained Release Quinidine Gluconate Tablet, *Biopharm. Drug. Dispos.*, 11(1):17 at 17 (1990) ("Rate of bioavailability was significantly enhanced following . . . [a] LF [Low Fat] meal as compared to that of the other treatment groups . . . [High Fat meal and a fasting control].") (Exhibit D). Similarly, it was determined that a high-fat diet decreased the peak plasma concentration (Cmax) of cefaclor more than a low-fat diet. *See* S. Karim, et al., The Effect of Four Different Types of Food on the Bioavailability of Cefaclor, *Eur. J. Drug. Metab. Pharmacokinet.*, 28(3):185 at 189 (2003) ("$AUC_{0\text{-}inf}$ values were significantly different for high-fat non-vegetarian vs low-fat non-vegetarian [diets].") (Exhibit E).

[6] Conversely, a person might eat a high fat breakfast (bacon, eggs with butter, fried hash browns, toast with cream cheese, whole milk), a low fat lunch (salad with low fat dressing), and a high fat dinner (steak, french fries, ice cream).

Conversely, other studies have shown that high fat diets have a greater effect in enhancing the bioavailability of certain drugs than low fat diets. *See* Gupta, et al., Effect of Food on the Pharmacokinetics of Cyclosporine in Healthy Subjects Following Oral and Intravenous Administration, *J. Clin. Pharmacol.*, 30(7):643 at 647 (1990) ("bioavailability measures [with high fat meals] were significantly higher than the corresponding values during the low fat phase.") (Exhibit F); Doose, et al., Effects of Meals and Meal Composition on the bioavailability of Fenretinide, *J. Clin. Pharmacol.*, 32(12):1089 at 1089 (1992) (". . . the bioavailability of fenretinide, as assessed by total area under the plasma concentration curve, was three times greater after the high-fat meal than after the high-carbohydrate [low-fat] meal.") (Exhibit G); Uematsu, et al., Effect of Dietary Fat Content on Oral Bioavailability of Menatetrone in Humans, *J. Pharm. Sci.*, 85(9):1012 at 1012 (1996) ("The area under the plasma menatetrone concentration-time curve within the first 24 hours (AUC_{0-24}) increased with increase in fat content.") (Exhibit H). In particular, it was determined that a high fat diet has a greater effect in enhancing the bioavailability of some water insoluble drugs than a low fat diet. *See* Ogunbana, et al., Fat Contents of Meals and Bioavailability of Griseofulvin in Man, *J. Pharm. Pharmacol.*, 37(4):283 at 283 (1985) (". . . the higher the fat content of the meals the higher the enhancement of the bioavailability of griseofulvin in man.") (Exhibit I).

It should also be noted that none of these studies reported evidence of any clinical relevance of bioavailability resulting from food-drug interactions and none of the drugs discussed have approved dosing instructions that require either fed or fasted dosing. In fact, one study on cyclosporine determined that although a higher fat content increased cyclosporine bioavailability and clearance, this phenomenon was of no clinical importance because the pharmacodynamics of the drug were not affected significantly. *See* Tan, et al., Effect of Dietary Fat on the Pharmacokinetics of Cyclosporine in Kidney Transplant Recipients, *Clin. Pharmacol. Ther.*, 57(4):425a t 425 (1995) ("An increased fat content of food significantly increases cyclosporine bioavailability and clearance. However, this is unlikely to be of clinical importance . . . .") (Exhibit J).

Food-drug interactions are also affected by varying protein levels. Studies have shown that foods with high protein and no fat content do not result in a significant bioavailability increase of some water insoluble drugs, whereas fat content affects the absorption of the same drug. *See* Shargel, et al., Applied Biopharmaceutics and Pharmacokinetics, McGraw-Hill/Appleton & Lange, 128, 3d ed. 2004 (". . . drugs, such as griseofulvin are better absorbed when given with food containing a high fat content.") (Exhibit K). Significantly, metaxalone has low solubility. *See* Declaration of Leslie Z. Benet, Ph.D. at 4 (Exhibit 10 to King Citizen Petition).

Yet another issue of great importance that affects drug absorption is the effect that different types of food may have on gastric emptying. Studies have shown that gastric emptying and, consequently, the rate and extent of drug absorption are influenced by the volume, type of meal, and physical state of the gastric contents. *See* Shargel, *supra* at 126 (Table 7-4) (Exhibit K). King's studies also fail to account for the effect of different food types on gastric emptying times and the potential effect thereof on the bioavailability of metaxalone.

Because King has not considered the potential effects of the type of food with which metaxalone is dosed, its conclusory claims about enhanced or more consistent bioavailability of Skelaxin when taken with food are not a sufficient basis for FDA to approve a general fed-dosing instruction. However, dosing on an empty stomach would remove any effect of meal-to-meal variation in fat, protein and carbohydrate consumption, and its attendant effect of varying the blood levels of metaxalone.

(b) The Skelaxin Bioavailability Study Results Are Ambiguous and Potentially Confounding

King's attempt to support its requested fed dosing instruction by claiming that it would ensure more consistent blood levels (whether compared to fasted dosing, or to uncontrolled dosing) is not supported by the description of the studies and results included in King's Citizen Petition. As King describes it, its biostudies and meta-analysis show that:

> (1) in the fed state, regardless of gender, age has little or no effect upon the bioavailability of Skelaxin;
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> (2) in contrast, in the fasted state, regardless of gender, bioavailability is statistically significantly increased with an increase in age; and
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> (3) in both the fed and fasted states, bioavailability is statistically significantly higher in females than in males.[7]

King Citizen Petition at 8. However, King glosses over the fact that fed-dosing does increase bioavailability (as shown in the initial Elan studies), and that therefore even in scenario 1 above, young and old fed subjects must have experienced increased bioavailability. In evaluating the "consistency" of blood levels between groups, it would therefore be necessary to compare the magnitude of the increased bioavailability in older fasted subjects (scenario 2 above) with that in older fed subjects (scenario 1 above).[8] However, King fails to disclose the comparative increases between these two groups. Thus, King's description does not preclude the possibility that for older patients, the increase in bioavailability is greater in the fed state than in the fasted state, whereas younger subjects only experience increased bioavailability in the fed state. If that is the case, greater consistency among groups may not be achieved by fed-dosing.

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[7] In contrast to the initial Elan studies, and the age-related bioavailability study, each of which studied subjects in both fasted and fed (high fat) states, the gender study only included fasted subjects. King Citizen petition at 6-8.

[8] If food increases bioavailability in older subjects more than the increase observed in fasted older patients, it would seem to be more logical to require fasted dosing for older patients in order to blunt the rise in bioavailability (*if* one were to assume clinical significance of the food effect, which as discussed above would be an erroneous assumption).

Moreover, although when dosed fasting, older patients reportedly had increased plasma levels, King does not disclose how variable the increase was for those affected subjects. Since consistency is King's alleged goal in advocating fed-dosing, King's failure to even assert that the fed dosing effect in older subjects occurred in a narrow and predictable range casts doubt as to whether its studies truly support greater blood level consistency. King's studies may also fairly be questioned due to the fact that King does not disclose the relevant age range in which the purported age effect was observed, nor how many subjects in its study experienced this age-effect. Given the small size of the age study (44 subjects), the wide age ranges studied (18-81), and the known high variability of the food effect (see below), it is a dubious conclusion indeed that this study adequately demonstrated that fed dosing achieves meaningfully "more consistent" plasma levels in patients generally, in individual patients from day to day, or in any age-based subgroup.

In addition, King's assertion that its studies support greater blood level consistency when metaxalone is dosed in the fed state appears to be contradicted by the currently approved Skelaxin labeling's description of the initial Elan biostudies. As shown in the Skelaxin labeling, the food effect is highly variable, with the mean Tmax under fed conditions actually overlapping the entire Tmax range (for a 400 mg dose) under fasted conditions (2.1 – 4.5 hours fasted *versus* 2.0 – 6.6 hours fed (400 mg); and 1.8 – 4.2 hours fasted *versus* 2.6 – 7.2 hours fed (800 mg)). In other words, when dosed with food, Tmax can occur at any time within a range of 4.6 hours, compared to within a narrower range of 2.4 hours when dosed fasted. Moreover, Elan's initial studies showed that by some parameters there is actually relatively little food effect – indeed, fasted and fed dosing could be considered bioequivalent, as the $AUC_{0\text{-}inf}$ of either a 400 mg or an 800 mg dose when administered in the fed state is within the 80% – 125% range of fasted dosing. This variability and ambiguity of the observed food effects in the Elan studies reflects that King has failed to adequately establish that fed dosing achieves more consistent blood levels.

Finally, it is also important to note that food-effect studies do not necessarily reflect the true pharmacokinetics of a drug in real-world settings. For instance, Leslie Z. Benet, Ph.D., one of King's paid consultants, has described a food-effect study of cyclosporine which showed lower variability of bioavailability (i.e., more consistent blood levels) compared to other cyclosporine studies. See Gupta, SK, Manfro, RC, Tomlanovich, SJ, Gambertogilio, JG, Garovoy, MR, Benet, LZ, *J. Clin. Pharmacol.*, 30(7):649 (1990). This discrepancy, as explained by Dr. Benet and his co-authors, "could be due to the standardization of diet employed [in the described study]. . ., as well as the absence of other coadministered drugs which might influence the kinetics of . . . [the drug]." More generally, Dr. Benet and his colleagues concluded, "The observed variability in clearance, bioavailability, and volume of distribution values for cyclosporine across various pharmacokinetic studies can be partially accounted [for] by the type of food administered and the sampling matrix used for analysis." *Id.* at 643 (abstract) (emphasis added). Thus, King's own consultant would apparently agree that the Elan studies – which used a standardized diet – cannot reliably support the contention that a fed dosing instruction would lead to more consistent blood levels of metaxalone, especially given the varying dietary patterns of actual patients in uncontrolled real-life settings.

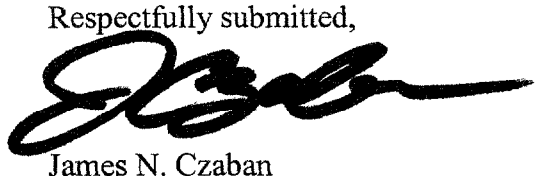
CONCLUSION

As shown above, King has not met even the minimum possible standard for supporting its proposed new dosing and administration instructions. There is no clinically relevant benefit to fed dosing, nor any detriment to either uncontrolled dosing (vis a vis meals) or fasted dosing. The Elan/King studies are wholly inadequate to support a generalized fed-dosing instruction because the studies failed to take account of variable bioavailability effects due to variations in the *type* of food that would be consumed by actual patients taking metaxalone with meals. Nor has King provided adequate support for the conclusion that fed dosing would ensure greater blood level consistency for metaxalone users. Thus, FDA should refuse to approve King's fed-dosing sNDA.

However, if FDA were nevertheless to determine that new food-related dosing and administration instructions are desirable (despite the lack of clinical relevance), the only medically rational approach would be to require the Skelaxin labeling to instruct all patients to take the drug on an empty stomach. Such a dosing instruction would more reliably minimize blood level variations in the metaxalone patient population generally, and in individual patients with variable dietary patterns.

For the reasons discussed herein, there is no basis for FDA to approve a fed-dosing instruction in the Skelaxin labeling. FDA therefore should grant Mutual's Stay Petition, and refuse to approve King's sNDA.

Respectfully submitted,



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